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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	766.44	1416

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EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/855,587

Applicant(s)

SASAI ET AL.

Examiner

Joseph T. Weitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-87 is/are pending in the application.
- 4a) Of the above claim(s) 56, 57 and 76-79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 14, 15, 18-24, 26, 27, 72, 74, 75 and 80-87 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 3/31/2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This application claims benefit to provisional application 60/257,049, filed December 20, 2000, and to foreign applications: 1000-144059, filed May 16, 2000; and 2000-290819, filed September 25, 2000, both filed in Japan.

Applicants amendment filed May 3, 2006, has been received and entered. Claims 2-14, 16, 17, 25-55, 58-71 and 73 have been cancelled. Claims 1, 15, 18-19, 21, 23, 24, 56, 57, 72 have been amended. Claims 80-87 have been added. Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-87 are pending.

Election/Restrictions

An election of species was required, in particular the species of (C) ectodermal cell (and generally with respect to the other species to cells of the nervous system) and the species of (Q) BMP4 was elected (see election page 2). It is noted that the elected species of cell type has been amended and narrowed in scope to a specific ectodermal cell type, specifically, a neural stem cell or a nerve cell (see claim 1, line 2). Also, the claims have been amended to delete the embodiment for use of specific components, i.e. "or stromal cell derived factor" (see claim 1, and dependent claims) and now only encompass the use of a stromal cell, originally species (t) in the species election (see page 23 of restriction requirement). The elected invention encompasses a method of inducing differentiation of an embryonic stem cell comprising culturing said ES cell under non-aggregation conditions, without retinoic acid and in the presences of a stromal cell (species t) are under consideration.

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Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-87 are pending. Claims 56, 57 and 76-79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. See office action mailed January 16, 2003. No new arguments have been presented.

Newly added claims 80-87 encompass the production of specific cell types and/or use of specific ES and stromal cell lines, therefore will be examined with the elected invention.

Claims 1, 14, 15, 18-24, 26, 27, 72, 74-75, 80-87 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 15, 18-24, 26, 27, 72, 74-75, 80, 82-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

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the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The present claims have been amended to recite and encompass a method that has a pre-culturing step and a subsequent culturing step. Literal support for "pre-culturing" and what is encompassed by this can not be found in the present specification. Moreover, figurative support for such a step wherein it results in "differentiation of embryonic stem cell into a nervous system cell before determining of dorso-ventral axis" can not be found, and appears to be inconsistent with the teaching of the present specification. More specifically, it appears to the BMP-4 in the absence of RA that is defining to the culture media affecting the embryonic stem cell to differentiate preferentially into a neural cell lineage. Review of the specification of for support of a cell and the term "dorso-ventral axis" appears to only support the differentiated cell type contemplated (see paragraphs 62 or 195, and original claim 10 for example), not a cell that exists in some pre-culture condition. It is noted that Applicants fail to point to any specific support for the present claim amendments.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1, 14, 15, 18-24, 26, 27, 72, 74-75, 80, 82-87 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. As noted above, the pre-culturing step simply requires culturing without the addition of RA or BMP-4, however these conditions fail to

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provide the proper conditions where the embryonic stem cell differentiates in light of the teachings of the present specification. Moreover, it would be recognized in the art that culture conditions of an embryonic stem cell grown on a stromal cell feeder layer are those that maintain the undifferentiated state of the stem cell. Beyond failing to provide any guidance to practice the method as claimed, the methods are inconsistent with what is known in the art for culturing embryonic stem cells. It would constitute an undue amount of experimentation given the knowledge in the art, and the lack of guidance in the present specification to practice the method as claimed.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-75 stand rejected and newly added claims 80-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants summarize the basis of the rejection, and note the amendment to the claims to address the basis of the rejection. See Applicants' amendment pages 11-12. Applicants' arguments have been fully considered, but not found persuasive.

It is noted that the claims as amended require two steps pre-culturing and a subsequent culturing step that does recite that BMP-4 is added, however the first step fails to set forth the specific or particular requirement of "pre-culturing" in particular one that results in "differentiation of embryonic stem cell into a nervous system cell before determining of dorso-ventral axis" as recited in the claim(s) (see first step of claim 1 for example). Examiner acknowledges the amendment to the claims to include BMP-4, however this step appears to be more consistent with the formation of a cell of neural lineage than simply culturing the embryonic stem cell without RA and BMP-4. Again, claim 1 appears incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claim 26 and 27 rejected because there is insufficient antecedent basis for the limitation of specific cell types is withdrawn.

Cancellation of the claims has rendered the rejection moot.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-75 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for culturing embryonic stem cells on MC3T3-G2/PA6 stromal cells where in the cells are plated as isolated single cell cultures and allowed to proliferate and differentiate into rostral CNS cells, does not reasonably provide enablement for the use of stromal cells generically, nor for providing “a neural stem cell” or any general “nerve cell” as recited in the claims is withdrawn.

With respect to the deposit requirement of MC3T3-G2/PA6, Applicants’ supporting information provided in their response addresses the basis of this portion of the rejection. With respect to the use of any stromal cell, upon consideration of Applicants’ arguments and in view of the amendments to the claims, Examiner would agree that providing a stromal cell and conditions in which the embryonic stem cell does not form an embryoid body would be routine and are fully enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 81 is rejected under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* (Biol Reprod.1996 Aug;55(2):254-9).

Newly added claim 81 is directed to producing a neural stem cell which is anti-nestin positive by antibody staining, however the only active method step requires that an embryonic stem be cultured *in vitro* without RA or BMP-4 for 1 to 14 days, and that embryoid bodies not be formed during this period. Thomson *et al.* teach the isolation and characterization of embryonic stem cells from the Common Marmoset. In the characterization of the stem cells, Thomson *et al.* teach that the cells are cultured on a feeder layer for propagation of the cell lines. In addition, Thomson *et al.* teach that before the formation of embryoid bodies, the embryonic stem cells are cultured for a period of time before confluency and the induction of embryoid body formation (page 255). In each case, the media used does not contain RA nor BMP-4. Though Thomson *et al.* do not specifically analyze nor demonstrate the formation of nestin positive cells, clearly they have practiced the method step encompassed by the instant claim, and provide for the formation of neural stem cell.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re*

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Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In this case, the method as broadly claimed is anticipated by the method practiced by Thomson *et al.*

It is noted that to some extent that other pending claims if simply interpreted to encompass practicing the method step of pre-culturing and culturing steps as broadly encompassed by the instant claims could be interpreted to be anticipated by Thomson *et al.* More specifically, the steps of propagating the stem cells for a period of time in culture would be considered a step of pre-culture, and subsequent passages and culturing would be considered the second culturing step. However, a reasonable interpretation of the enabled teaching of Thomson *et al.* provides for methods where the stem cells are not differentiated neural stem cells or neural crest cells as required by the instant claims (i.e. “so that differentiation of embryonic stem cell into a nervous system cell” recited in claim 1 for example).

Conclusion

No claim is allowed.

Claims 1, 14, 15, 18-24, 26, 27, 72, 74-75, 80, 82-87 are free of the art of record because the art of record fails to teach the specifically claimed *in vitro* method pre-culturing and subsequent culturing wherein it results in the formation of a neural stem cell or nerve cell as required by the claims, however they are subject to other rejections. It is noted that retinoic acid is commonly used a factor to differentiate a pluripotent cell towards or into a neural cell lineage. In the instant case, the specification provides support for the instant claims which specifically exclude the use of retinoic acid, instead relying on the affect of BMP-4. However, the affect of

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BMP-4 appears to affect pre-conditioned cells in culture which are generated from embryonic stem cells.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

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Joseph T. Voitach

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